

Correcting human mitochondrial mutations with targeted RNA import.

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Public Summary:

Mutations in the human mitochondrial genome are implicated in neuromuscular diseases, metabolic defects, and aging. An efficient and simple mechanism for neutralizing deleterious mitochondrial DNA (mtDNA) alterations has unfortunately remained elusive. Here, we report that a 20-ribonucleotide stem-loop sequence from the H1 RNA, the RNA component of the human RNase P enzyme, appended to a nonimported RNA directs the import of the resultant RNA fusion transcript into human mitochondria. The methodology is effective for both noncoding RNAs, such as tRNAs, and mRNAs. The RNA import component, polynucleotide phosphorylase (PNPASE), facilitates transfer of this hybrid RNA into the mitochondrial matrix. In addition, nucleus-encoded mRNAs for mitochondrial proteins, such as the mRNA of human mitochondrial ribosomal protein S12 (MRPS12), contain regulatory sequences in their 3'-untranslated region (UTR) that confers localization to the mitochondrial outer membrane, which is postulated to aid in protein translocation after translation. We show that for some mitochondrial-encoded transcripts, such as COX2, a 3'-UTR localization sequence is not required for mRNA import, whereas for corrective mitochondrial-encoded tRNAs, appending the 3'-UTR localization sequence was essential for efficient fusion-transcript translocation into mitochondria. In vivo, functional defects in mitochondrial RNA (mtRNA) translation and cell respiration were reversed in two human disease lines. Thus, this study indicates that a wide range of RNAs can be targeted to mitochondria by appending a targeting sequence that interacts with PNPASE, with or without a mitochondrial localization sequence, providing an exciting, general approach for overcoming mitochondrial genetic disorders.

Scientific Abstract:

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